Reaction of (*Z*)-Ethylideneoxirane 7 with Lithium Di-*n*-butylcuprate. In the manner described above for the *E* isomer, a mixture of diastereomers **16** and **17** was produced in a 1/3 ratio, respectively. The infrared spectrum appeared identical with that of **16**, and the 270-MHz NMR spectrum had the following signals in addition to those present in the isomer **16**: ($CDCl_3$) δ 4.11 (2 H, br m), 2.45 (1 H, m), 1.03 (3 H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 144.37 (**17**), 144.04 (**16**), 130.21 (**16**), 130.00 (**17**, olefinic carbons).

Reaction of (*E*)-Pentylideneoxirane with Lithium Dimethylcuprate. To a stirred suspension of 8.55 g (45 mmol) of cuprous iodide in 150 mL of dry ether cooled to 0 °C was added dropwise 69.2 mL (90.0 mmol; 0.77 M solution) of methyllithium. After 10 min, 3.0 g (15.5 mmol) of (*E*)-pentylideneoxirane **5** was added in 30 mL of ether. After 40 min at 0 °C the reaction mixture was poured into a saturated ammonium chloride solution containing ammonium hydroxide (~pH 9). After the mixture was stirred for 10 min, the layers were separated, the aqueous layer was extracted with ether, and the organic layers were combined, washed with water, dried, and concentrated in vacuo. The residue was distilled (Kugelrohr) to give 3.05 g (94%) of a colorless liquid [bp 70 °C (0.02 torr)] consisting of 70% of **16** and **17** and 30% of **18** (VPC). Isomers **16** and **17** were separated from **18** (Waters Prep LC/500, 5% ether/hexane). The ratio of **16**/**17** was 85/15 as determined by integration of the multiplets at δ 2.45 and 2.58, respectively. Pentylidene alcohol **18** had the following physical properties: bp 60 °C (0.02 torr); IR (CCl_4) 3650-3375, 1458, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.19 (1 H, t, J = 7 Hz), 3.75 (1 H, d, J = 10 Hz), 3.13 (1 H, d, J = 10 Hz), 2.90 (1 H, m), 2.23-1.87 (3 H, m), 1.86-1.17 (10 H, br m), 1.12 (3 H, d, J = 7 Hz), 1.00 (3 H, s), 0.91 (3 H, t, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 145.07, 123.32, 70.40, 40.94, 34.85, 32.25, 31.73, 29.62, 26.78 (2 C), 22.37, 21.70, 16.72, 13.79. Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.83; H, 12.43.

(*E*)-Pentylidenealdehyde 19. To a stirred suspension of pyridinium chlorochromate (310 mg, 1.43 mmol) and anhydrous sodium acetate (117 mg, 1.43 mmol) in 6 mL of methylene chloride was added a solution of (*E*)-pentylidene alcohol **18** (150 mg, 0.71 mmol) in 5 mL of methylene chloride. After being stirred for 4 h at 25 °C, the reaction mixture was diluted with ether and filtered through a pad of Florisil over Celite 545. The solids were washed well with ether. Concentration of the organic layers afforded 140 mg (95%) of crude product as a colorless oil. Distillation afforded 130 mg (89%) of (*E*)-pentylidene aldehyde **19**: bp 50 °C (0.02 torr); IR (CCl_4) 2800, 2705, 1728, 1465, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.30 (1 H, s), 4.77 (1 H, t, J = 7 Hz), 2.95 (1 H, m), 2.22-1.92 (2 H, br m), 1.82-1.39 (6 H, br m), 1.31 (4 H, br m), 1.23 (3 H, s), 1.12 (3 H, d, J = 7 Hz), 0.91 (3 H, m); gas chromatograph-mass spectrum (70 eV), m/e (relative intensity) 208 (M^+, 2), 179 (90), 123 (100), 109 (75), 97 (22), 95 (56), 81 (65), 67 (23).

Acknowledgment. This research was supported by funds from the National Institutes of Health (CA16432) and Hoffman-LaRoche (Nutley) and by NIH Research Grant No. 1-P07-PR00798 (Bruker HX-270) from the Division of Research Sources. F.E.Z. expresses his appreciation for a Career Development Award (1973-1978) from the Division of General Medical Sciences (NIH-GM-70577).

Registry No. 2, 59697-64-2; **3**, 75731-75-8; (*E*)-**4**, 75731-76-9; (*Z*)-**4**, 75731-77-0; **5**, 75731-78-1; **6**, 43011-49-0; **7**, 75766-22-2; (*E*)-**8**, 75731-79-2; (*Z*)-**8**, 75731-80-5; **9**, 75731-81-6; **11**, 75731-82-7; **12**, 75731-83-8; **13**, 75731-84-9; **14**, 75766-23-3; **15**, 75731-85-0; **16**, 75731-86-1; **16** *p*-bromophenylurethane, 75731-87-2; **17**, 75731-88-3; **18**, 75731-89-4; (*trans*)-(*E*)-1,3-dimethyl-2-pentylidenecyclohexanecarboxaldehyde, 75750-99-1; 2-cyclohexenone, 960-68-7; *n*-valeraldehyde, 110-62-3; 4-*tert*-butyl-2-(hydroxymethylene)cyclohexanone, 22252-96-6; 4-*tert*-butyl-2-(pyrrolidinomethylene)cyclohexanone, 75731-90-7; methyl bromide, 74-83-9; *p*-bromophenyl isocyanate, 2493-02-9; (*TT*)-1,3-dimethyl-2-ethylcyclohexanol, 75731-91-8; (*CC*)-1,3-dimethyl-2-ethylcyclohexanol, 75766-24-4; (*CT*)-1,3-dimethyl-2-ethylcyclohexanol, 75766-25-5; (*TC*)-1,3-dimethyl-2-ethylcyclohexanol, 75766-26-6.

Reactions of α,β-Unsaturated Ketones with Hydrogen Sulfide. γ-Keto Sulfides or Tetrahydrothiopyranols?[1]

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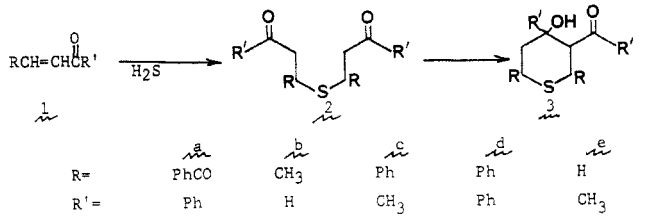
The reaction of several α,β-unsaturated ketones with H_2S under a variety of conditions has been investigated. With *trans*-1,2-dibenzoylethylene (**1a**) the tetrahydrothiopyranol **3a** is the only product, not the corresponding open-chain sulfide **2a** reported in the literature. The product from benzylideneacetone (**1c**) is the tetrahydrothiopyranol (**3c**) with the relative configuration at C-4 epimeric with that reported in the literature based on the observation of long-range coupling of the hydroxyl and C-5 axial hydrogen in one isomer. The "α-, β-, and γ-sulfides" reported from benzylideneacetophenone (**1d**) were shown to be (α-sulfide) a mixture of the diastereomeric sulfides **2d**, (β-sulfide) the tetrahydrothiopyranol **3d** with the stereochemistry **12**, once again based on long-range coupling of the OH and C-5 axial hydrogen, and (γ-sulfide) the tetrahydrothiophene **13**. From methyl vinyl ketone (**1e**) an authentic sample of the open-chain sulfide **2e** could be obtained with H_2S and cyclized with Na_2S to the tetrahydrothiopyranol **3e** as a mixture of epimers **21** and **22** whose structures were assigned from ^{13}C chemical shift data.

The base-catalyzed conjugate addition of H_2S to α,β-unsaturated ketones **1** to give γ-keto sulfides **2** appears to be a well-known reaction.[2] What is not well-known, however, is that sometimes sulfides such as **2** undergo a facile intramolecular aldol condensation to give tetra-



(1) Taken from the Ph.D. dissertation of D. Del Mazza, Texas Christian University, 1980.

(2) (a) A. Schöberl and A. Wagner in "Methoden der Organischen Chemie (Houben-Weyl)", Vol. IX, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p 21; (b) E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Vol. I, Chemical Publishing Co., New York, 1958, p 21; (c) G. C. Barrett in "Comprehensive Organic Chemistry", Vol. III, D. Neville Jones, Ed., Pergamon Press, New York, 1979, p 91.

0022-3263/81/1946-0128$01.00/0

Table I. ^{13}C NMR Values[a] for the Tetrahydrothiopyranols 3, 21, and 22 and the Tetrahydrothiophene 13

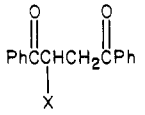
3a	3c	3d	21	22	13
203.4 (s)	216.3 (s)	207.0 (s)	213.9 (s)	210.8 (s)	
197.9 (s)					199.5 (s)
194.8 (s)					194.1 (s)
139.7	140.9 (s)	145.8			139.0
136.7	138.5 (s)	140.7			137.5
136.2		137.9			137.2
135.4					136.2
133.8					133.4
133.2		132.9			132.8
129.2					
128.8	128.9	128.4			128.6
128.4	128.2	127.7			127.9
128.1	127.2	127.1			127.4
125.5		124.8			
86.9 (s)	71.3 (s)	76.1 (s)	68.6 (s)	71.2 (s)	
57.8 (d, 136)	63.9 (d, 132)	58.3 (d, 132)	57.9 (d, 132)	60.1 (d, 132)	65.2 (d, 130)
55.8 (d, 149)	47.4 (d, 141)	48.5 (d, 153)			57.0 (d, 142)
52.4 (d, 146)	46.4 (t, 127)	47.0 (t, 129)			55.1 (d, 142)
38.8 (t, 127)	42.9 (d, 143)	43.5 (d, 149)	39.5 (t, 127)	42.0 (t, 129)	54.4 (d, 136)
	34.8 (q, 128)		31.5 (q, 128)	31.8 (q, 127)	
	30.1 (q, 126)		29.4 (q, 125)	27.6 (t, 140)	
			26.4 (t, 140)	25.8 (t, 137)	
			23.9 (t, 140)	22.5 (q, 125)	

[a] In $CDCl_3$ solution in parts per million downfield from Me_4Si. The multiplicities, when known, are shown in parentheses, together with the $^1J_{CH}$ value expressed in hertz.

hydrothiopyranols **3**. The one examle in the literature (**c** series)[3] has been widely ignored[4] in spite of an analogous case in the aldehyde series (**b**).[5] This paper describes three additional examples of this reaction, clarifies some erroneous structural assignments, and reports a totally new reaction of α,β-unsaturated ketones and polysulfides.

Results and Discussion

***trans*-Dibenzoylethylene (1a).**[6] The reaction of this ketone with H_2S is reported to give the sulfide **2a** on the basis of Raney nickel desulfurization to 1,2-dibenzoylethane and elemental analysis both of the compound itself and its *trioxime*.[7] Alternative syntheses from the chloro ketone **4a**[8] and several disulfides, **4b**,[9] appear to further

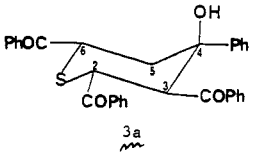


4a, X = Cl
b, X = SSR
c, X = Br
d, X = SH

support the assigned structure **2a**. Under a variety of conditions including the original ones[7] and from the bromo ketone **4c**, the same substance was obtained in our laboratory in yields as high as 93%. The EI and the CI mass spectra are consistent with either the sulfide **2a** or the tetrahydrothiopyranol **3a** structure since they are essentially a superposition of the fragmentations of the unsaturated ketone **1a** and the mercapto ketone **4d** which could originate from either a β elimination or a retro-aldol reaction plus a β elimination of the compound. The remaining spectral properties are inconsistent with the sulfide structure **2a**, however, and clearly indicate that this substance is the tetrahydrothiopyranol **3a**.

The infrared spectrum displays two conjugated carbonyl peaks at 1665 and 1680 cm^{-1} and a sharp OH peak at 3500 cm^{-1}. The best evidence for the structure **3a**, however, is obtained from the proton NMR spectrum. The upfield portion of the spectrum shows an ABX pattern, which can be assigned to the CH_2CH system on the less substituted side of the molecule. The methylene hydrogens observed at 3.10 and 3.62 ppm show a geminal coupling constant of 18 Hz and couplings to the methine hydrogen (H_6) of 3 and 10 Hz, respectively, the first one indicating an axial-equatorial and the second one an axial-axial relationship.[10] The methine hydogen H_6 observed at 4.51 ppm must therefore occupy an axial position, thus placing the benzoyl group equatorially.

The AB quartet expected for the more substituted side of the ring (H_2 and H_3) is observed at 5.41 ppm, with a measured J_{AB} of about 11 Hz, indicating an axial–axial relationship. Hence, all benzoyl groups occupy equatorial positions, as could be expected. If the 4-phenyl group is assumed also to be equatorial then the conformation of **3a** can be written as shown.



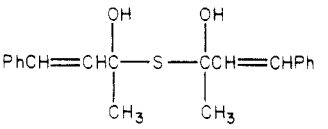
3a

Additional evidence comes from the ^{13}C NMR spectrum (Table I), which shows three different carbonyl carbons around 200 ppm[11] and four different phenyl ipso carbons

(3) G. C. Forward and D. A. Whiting, *J. Chem. Soc. C*, 1647 (1969).
(4) According to "Science Citation Index" (the Institute of Scientific Information, Philadelphia, PA) there were no citations to ref 3 through 1979. A brief discussion of the results of this research does appear in ref 2c, p 29, but without attribution.
(5) (a) F. Asinger and M. Fischer, *J. Prakt. Chem.*, [4] **35**, 81 (1967); (b) R. J. C. Kleipool, A. C. Tas, H. Maarse, R. Neeter, and H. T. Badings, *Z. Lebensm.-Unters.-Forsch.*, **161**, 231 (1976).
(6) A preliminary report of these results was presented at the 32nd Southwest Regional Meeting of the American Chemical Society, Fort Worth, TX, Dec 1976, Abstract No. ORGN 12.
(7) E. Campaigne and W. O. Foye, *J. Org. Chem.*, **17**, 1405 (1952).
(8) R. G. Hiskey and J. A. Kepler, *J. Org. Chem.*, **29**, 3678 (1964).
(9) R. G. Hiskey and A. J. Dennis, *J. Org. Chem.*, **33**, 2734 (1968).
(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, New York, 1969, p 288.

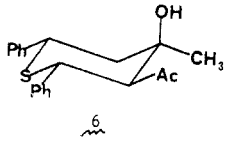
between 139.7 and 135.4 ppm.[11] A signal at 86.9 ppm remains a singlet in the H-coupled spectrum and is therefore assigned to C-4. The methylene C-5 is similarly found to resonate at 38.8 ppm. The remaining three signals are found at 52.4, 55.8, and 57.8 ppm. The first two show a $^1J_{CH}$ of 146 and 149 Hz, as compared to 136 Hz for the third, and are thus assigned to C-2 and C-6. It is known, in fact, that proximity to an electronegative atom increases the size of the C–H coupling constant.[12]

Benzylideneacetone (1c). The reaction of this ketone with H_2S was first studied by Fromm, who isolated a compound to which he assigned the structure of a "duplobenzylideneacetone monosulfide", **5**.[13] The more

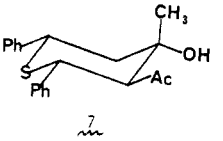


5

reasonable sulfide structure **2c** was proposed some years later[14] and the correct tetrahydrothiopyranol formulation **3c** more recently still.[3] The latter researchers also were able to prepare the authentic open-chain sulfide **2c** from the ketone **1c** and H_2S/Et_3N and then cyclize it with base to **3c**. These results were confirmed in our laboratory, including the use of Na_2S as a base in the last reaction. The stereochemistry of the tetrahydrothiopyranol **3c** also was clarified by proton NMR and shown to be **6** rather than the epimeric **7** previously suggested with reservations.[3]

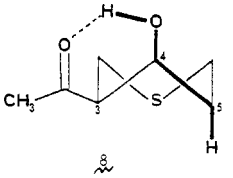


6



7

The experimental basis for this revision rests on the observation that the axial hydrogen of the methylene group of the major, higher melting, isomer of **3c** shows long-range coupling with the hydroxyl hydrogen, with a coupling constant of about 1.8 Hz. This was confirmed by computer spin simulation. Only by assuming such long-range coupling could the AB part of the apparent ABX system be correctly reproduced. Furthermore, D_2O exchange removed this coupling, as expected, and reduced the system to a true ABX pattern, as confirmed by spin simulation. The size of the coupling constant in this four σ bonds long range coupling strongly indicates a zigzag arrangement of the four bonds (W rule).[15] Such an arrangement is possible if the OH group is axial and the OH proton points toward the carbonyl, as in H-bonding (**8**, phenyls omitted).

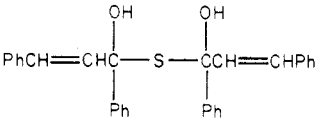


8

Similar observations have also been made with the tetrahydrothiopyran **3d** (see ahead), in which phenyl groups replace the methyls, and thus further support the above interpretation.

The revised structure of the major isomer formed in the presumably thermodynamically controlled aldol cyclization of **2c** is consistent with its expected greater stability compared to the 4-epimer, **7**, on the basis of the relative *A* values of methyl and hydroxyl.[16] The previous, tentative suggestion of **7** rather than **6** as the structure of this compound was based on a shorter OH···O=C distance in its Dreiding model and the reasonable assumption that this would lead to stronger intramolecular H bonding as is observed in the major isomer.[3] A reexamination of these models, however, reveals that in order to effectively H bond with an equatorial OH function as in **7**, the acetyl group must adopt a conformation approximately coplanar with the thiopyran ring, with its methyl group protruding into the adjacent 2-phenyl group. The resulting steric repulsion is likely to be underestimated by Dreiding models and is apparently sufficiently great to interfere with efficient intramolecular H bonding. Since the epimer **6** with an axial OH group lacks this steric interference, stronger intramolecular H bonding results.

Benzylideneacetophenone (1d). Fromm also studied the base-catalyzed reactions of this ketone with H_2S and could obtain three different "duplobenzylideneacetophenone monosulfides" (α, β, and γ) which were clamied to be the three possible geometrical isomers of **9**.[17] When



9

this structure was revised to that of the normal sulfide **2d**, it was recognized that only two diastereoisomers were possible, and so the existence of additional enolized forms was suggested.[14] Each of these "isomers" has now been resynthesized and their correct structure determined.

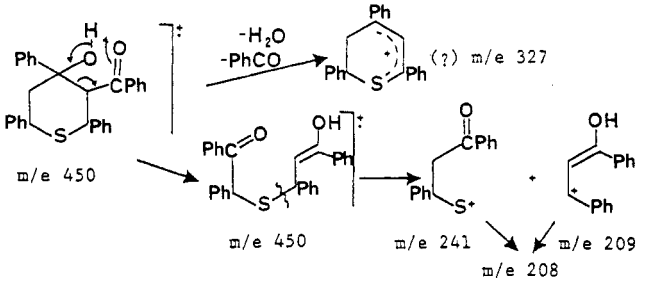
Fromm's "α-sulfide" was obtained from the ketone **1d** upon treatment with H_2S/Na_2S or more conveniently with H_2S/Et_3N in ether at atmospheric pressure. If the latter reaction is carried out in ethanol or under pressure, the β-mercapto ketone **10** is formed along with the disulfide **11**.[18] The NMR spectrum of the crude "α-sulfide" suggests that it is an approximately 1:1 mixture of the two possible diastereoisomers of **2d** which were separated by their different solubilities in $CHCl_3$/EtOH and found to have very similar melting points (95–100 and 102–104 °C; both were slightly contaminated with the other even after crystallization). In the proton NMR the diastereotopic CH_2 hydrogens show accidental equivalence and appear as doublets at 3.38 and 3.53 ppm, respectively. The methines are slightly broadened triplets at 4.22 and 4.50 ppm.

The infrared spectra also show differences. Particularly evident is the fact that three medium-strength absorptions at 1260, 1225, and 1205 cm^{-1} in the higher melting compound are replaced by a single strong absorption at 1225 cm^{-1} in the other isomer. The C=O band at 1685 cm^{-1} is also sharper than that in the former compound.

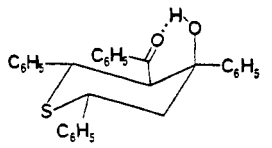
The "β-sulfide" was formed by treatment of the mercapto ketone **10** with an excess of NH_3 according to

(11) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, pp 81, 113.
(12) Reference 11, p 57.
(13) E. Fromm and H. Höller, *Ber Dtsch. Chem. Ges.*, **40**, 2982 (1907); E. Fromm and F. Haas, *Justus Liebigs Ann. Chem.*, **394**, 290 (1912).
(14) B. H. Nicolet, *J. Am. Chem. Soc.*, **54**, 1998 (1932).
(15) Reference 10, p 335.
(16) F. R. Jensen and C. H. Bushweller in "Advances in Alicyclic Chemistry", Vol. III, H. Hart and G. J. Karbatsos, Eds., Academic Press, New York, 1971.
(17) E. Fromm and E. Hubert, *Justus Liebigs Ann. Chem.*, **394**, 301 (1912).
(18) H. Tanaka and A. Yokoyama, *Chem. Pharm. Bull.*, **8**, 280 (1960).

Scheme I



Fromm[17] or by reaction of the "α-sulfide" **2d** with a catalytic amount of Na_2S in absolute EtOH. Spectroscopic evidence to be discussed below indicates that the "β-sulfide" is the tetrahydrothiopyranol **3d** with the stereochemistry **12**.



12

The infrared spectrum shows the OH absorption around 3450 cm^{-1}. The low carbonyl absorption at 1645 cm^{-1}, compared with the more normal 1658 cm^{-1} value of the open isomer **2d**, indicates that it is involved in H bonding.[19] The same effect was observed in **3c**, where the carbonyl absorption was found at 1690 cm^{-1} instead of at 1715 cm^{-1}.[19] In **3a** this effect was not apparent but cannot be ruled out, since the presence of three carbonyl functions in the molecule led to a broadened absorption, which could mask the shift due to H bonding.

The mass spectrum of **3d** shows a weak molecular ion which loses H_2O and subsequently PhCO to give a peak at m/e 327. Ring opening by a McLafferty rearrangement followed by α cleavage may account for the peaks at m/e 241 and 209, either of which can produce the ions at m/e 208 (Scheme I).

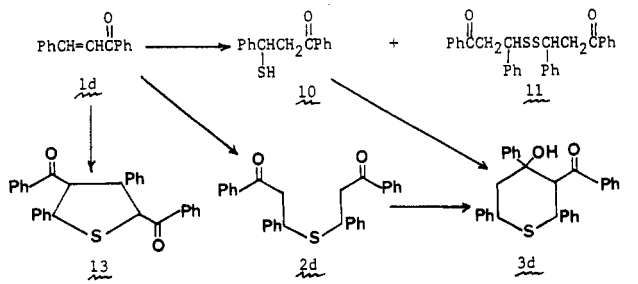
In the proton NMR the ABX system appears as two multiplets, centered at 2.40 (2 H) and 4.8 ppm (1 H). The latter multiplet is superimposed on the downfield doublet of the AB system, centered at 4.85 ppm, and shows a vicinal coupling constant of 11 Hz. The 2-phenyl and benzoyl groups are therefore equatorial. Computer spin simulation of the ABX system showed the presence of long-range spin coupling between the OH hydrogen and the axial methylene hydrogen in a manner totally analogous to that for **3c**. The calculated coupling constants are J_{AB} = 14 Hz (geminal coupling), J_{AX} = 3 Hz (axial-equatorial), J_{BX} = 11 Hz (axial-axial), $J_{B\text{-}OH}$ = 2 Hz (long-range coupling). From these data, therefore, one can conclude that the 6-phenyl group is also equatorial and, by analogy to **3c**, that the OH group is axial. The aromatic hydrogens are all found between 6.7 and 7.3 ppm, a remarkably high-field position,[20] which, at least for the three adjacent phenyls, is probably due to their mutual shielding in the closely packed arrangement.

The data from ^{13}C NMR are reported in Table I and further confirm the structure **3d** as well as its correlation to **3a** and **3c**.

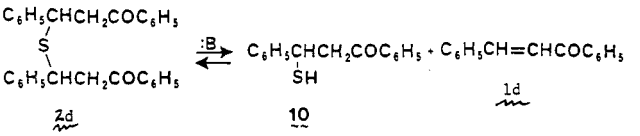
It is significant to note that the same diastereomer of **3d** was obtained from either diastereomer of **2d**, indicating

(19) K. Nakanishi and P. H. Solomon, "Infrared Absorption Spectroscopy", 2nd ed., Holden-Day, San Francisco, 1977, p 233.
(20) Reference 10, p 202.

Scheme II



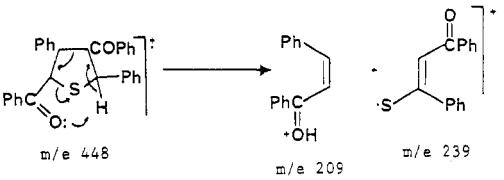
that equilibration occurs prior to cyclization probably via elimination to the thiol **10** and the olefin **1d**. The ease



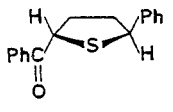
of the base-induced mercaptide elimination of β-keto sulfides is well-known.[18,21] The absolute preference for ring closure to **12** must derive from the equatorial arrangement of all bulky groups. The stereochemistry of **12** indicates that it is derived from the meso form of the sulfide **2d**, since the *dl* isomer would place the 6-phenyl group in the axial position.

The reaction of ketone **1d** with a saturated solution of sodium polysulfide in absolute EtOH, in the manner described by Fromm,[7] yielded a white solid whose melting point of 206–208.5 °C was similar to the 212 °C reported for the "γ-sulfide." The tetrahydrothiophene structure **13** proposed for this compound (Scheme II) on the basis of the spectral data to be discussed has a molecular weight of 448 as opposed to 450 for the true sulfide, a small enough difference to be undetected by the elemental analysis performed by Fromm.[17]

The strongest proof of the five-membered nature of the ring is found in the ^{13}C NMR spectrum (Table I) in which only four aliphatic carbons are observed. Besides loss of benzoyl from the molecular ion, the major mass spectrometric fragmentation generates the two fragments of m/e 209 and 239. Their origin is rationalized by a facile H



transfer which suggests that the phenyl and benzoyl groups α to the sulfur have an anti arrangement, as shown in **14** (β groups not shown). The stereochemistry of the β groups is not known.



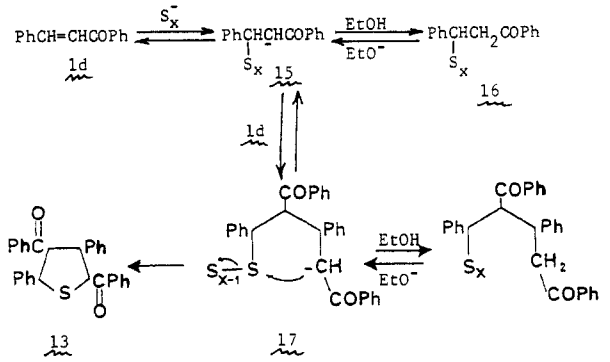
14

The infrared spectrum shows two carbonyl absorptions at 1690 and 1670 cm^{-1} and a strcng band at 1200 cm^{-1}.

In the proton spectrum the ring hydrogens appear as unresolved multiplets centered at about 4.66 (2 H), 5.02 (1 H), and 5.16 ppm (1 H). In the aromatic region, only two ortho hydrogens of the benzoyl groups are found at

(21) B. H. Nicolet, *J. Am. Chem. Soc.*, **53**, 3066 (1931).

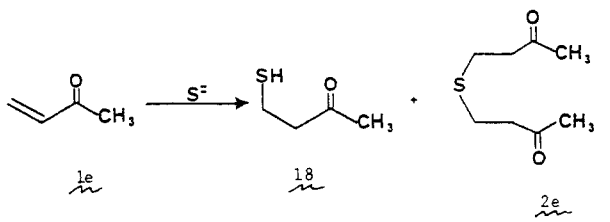
Scheme III



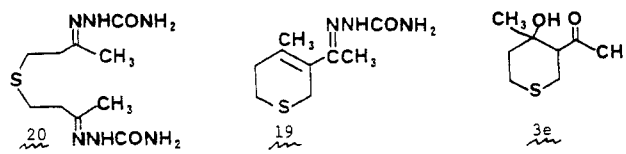
their normal position (~7.75 ppm), while the other two are upfield in the remaining aromatic multiplet. By analogy to the NMR spectrum of **3d**, this may arise from the benzoyl group in the β position being sandwiched between two phenyl groups, so that its protons are in a shielding zone.

The mode of formation of **13** must take into account the reaction medium. A saturated solution of sodium polysulfide in EtOH, formed by alternate additions of Na_2S and S_8 to EtOH until the initial volume of solvent is about doubled in the final dark red solution, consists of species of the general structure Na_2S_x, where x varies between 2 and 5, depending on the initial ratio of monosulfide and sulfur.[22] Michael addition of polysulfide S_x^- to ketone **1d** forms anion **15** which may be protonated to **16**, but only reversibly in the absence of water (Scheme III). Dilute polysulfide solutions gave no product, presumably because of the Le Chatelier principle acting on the equilibria between **1d**, **15**, and **16**. Another Michael addition of **15** to **1d** generates the anion **17** which is subject to the same equilibrium considerations as **15**. Now, however, an intramolecular nucleophilic displacement on S with a polysulfide anion, S_{x-1}^-, as the leaving group, generates the final product **13** irreversibly, presumably due to its stability toward ring opening and/or its insolubility in the solution.

Methyl Vinyl Ketone (1e). The reaction of this, the simplest possible α,β-unsaturated ketone (**1e**), with Na_2S is reported[23] to give two products, the mercaptan **18** and

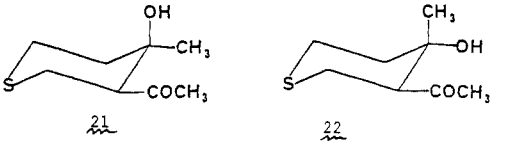


what was claimed to be the sulfide **2e** on the basis of the melting point (226–227 °C) of its "disemicarbazone". The cited comparison,[24] however, is to a monosemicarbazone (mp 227–228 °C) which was formulated as the dehydrated aldol product **19**. Since no spectral data were reported



in either of these papers,[23,24] however, the structure of the alleged sulfide **2e** remains open to question. An authentic sample of this sulfide was obtained in the present study by simply bubbling H_2S into an ethanol solution of the ketone **1e**, and the structure was verified as **2e** from its ^{13}C (only four different carbons) and ^1H NMR spectra [δ 2.52 (m, 4), 1.88 (s, 3)]. By use of a standard procedure,[25] a semicarbazone (mp 189–91 °C) was obtained which appears to be the authentic disemicarbazone **20** from its elemental analysis and ^{13}C NMR, which shows only five different kinds of carbon atoms.

Attempted cyclization of **2e** in absolute ethanol using either anhydrous NH_3 or Et_3N as a base gave mainly acid-soluble products. With Na_2S as the base, however, a product was obtained whose ^{13}C spectrum (Table I) had 15 aliphatic and two carbonyl carbon atoms, twice as many as would be expected for **3e**, thus indicating that two isomers of this compound might be present. Indeed, careful column chromatography separated two noncrystalline isomers of **3e**, **21** and **22**, in yields of 28% and 15%,



respectively. Mass spectroscopy confirmed their identical molecular weights (174, M^+) and displayed fragmentation patterns similar to those of **3d** ($-H_2O$, -acetyl and McLafferty rearrangement/α fission).

The infrared spectra are consistent with the cyclic structures and show clear differences for the two isomers. The OH absorption for **21** is sharper than that for **22**, closely resembling that of the other thiopyranols in this study. Both carbonyl absorptions are observed at 1695 cm^{-1}, indicating strong H bonding, but, again, **21** gives a sharper absorption than **22**. A more characteristic difference between the two isomers is the two medium-strength absorptions at 1370 and 1310 cm^{-1} in **21** but not **22**. These same two bands are also present in the infrared spectrum of **3c**.

Although the ^1H NMR's of **21** and **22** are very similar and do not lend themselves to easy analysis, definitive information about the structure and configurations of the two isomers was obtained from their ^{13}C NMR spectra (Table I). All aliphatic carbon resonances of **22** are downfield compared to those of **21**, except for the 4-methyl group which is upfield by almost 7 ppm. This observation suggests that **21** and **22** are epimers with the 4-methyl group equatorial and axial, respectively, and is based on two correlations: cyclohexane ring carbons consistently absorb at higher fields in the epimer with an axial OH group,[26] and methyl groups of cyclohexanes resonate at higher fields when they are axial.[27] The greater bulk of methyl over hydroxyl groups[16] also predicts that **21** would be the most stable isomer and hence the major one formed in an aldol condensation as is observed. Finally, the R_f of **21** on silica gel chromatography is higher than that of **22**, consistent with stronger intramolecular H bonding and hence weaker adsorption on the silica.

Conclusions

Several additional α,β-unsaturated carbonyl compounds such as mesityl oxide, cinnamaldehyde, α-methylcinnam-

(22) T. G. Pearson and P. L. Robinson, *J. Chem. Soc.*, 1473 (1930).
(23) N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2346 (1964).
(24) N. A. McGinnis and R. Robinson, *J. Chem. Soc.*, 404 (1941).
(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, 1964, p 253.
(26) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, p 165.
(27) Reference 26, p 66.

aldehyde, methyl cinnamate, and methyl crotonate were treated with Na_2S, and no evidence for thiopyranol formation was obtained. This should not be construed to mean that these compounds will not form the corresponding thiopyranols but only that the appropriate conditions were not used. As can ben seen from the studies described in this paper, relatively small changes in reaction conditions or reagents can tip the balance as to whether mercaptans, sulfides, or tetrahydrothiopyranols are obtained from α,β-unsaturated ketones and H_2S.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories. Infrared (IR) spectra were recorded on a Beckman 33 or a Perkin-Elmer 237 instrument. The IR spectra of liquid samples were taken as thin films between NaCl cells, and those of solids were obtained in a KBr matrix. Values are expressed in reciprocal centimeters.

Mass spectra were obtained on a Finnigan 4000 or Finnigan 1020 OWA gas chromatograph/mass spectrometer at an electron energy of 70 eV and are expressed as m/e (relative intensity) values. Chemical ionization (CI) mass spectra were taken on a Finnigan 4000 through the kindness of Mr. Paul Kelley of the Finnigan Instrument Co.

Proton magnetic resonance (^{1}H NMR) spectra were obtained on a JEOL JNM-MH-100 NMR spectrometer (100 MHz) unless otherwise indicated. Chemical shifts relative to internal Me_4Si are expressed in parts per million on the δ scale. First-order coupling constants (J) are apparent, unless otherwise indicated, and are given in hertz. Computer spin simulations were carried out on a JEOL JNM-FX-60 Fourier transform instrument, with the program supplied by the instrument manufacturer. See the paragraph at the end of the paper about supplementary material.

^{13}C nuclear magnetic resonance spectra were obtained with a JEOL JNM-FX-60 Fourier transform NMR instrument (60 MHz). Chemical shifts are in parts per million downfield from internal Me_4Si.

Reaction of *trans*-Dibenzoylethylene (1a) with $Na_2S·9H_2O$. The pH of a solution of $Na_2S·9H_2O$ (6.85 g, 28.5 mmol) was maintained at 9–10 with concentrated HCl while a solution of 5 g (21.2 mmol) of *trans*-dibenzoylethylene (**1a**) in 100 mL of THF was added dropwise with vigorous stirring over a period of 40 min. The precipitate was removed by filtration and the organic phase of the filtrate evaporated to dryness. The two solid crops were combined to give 5 g (93%) of white product **3a**, which was crystallized from 350 mL of CH_3CN: mp 191–194 °C (lit.[7] mp 188–192 °C); IR 3500, 3415 (br, sh), 3080, 1680, 1665, 1602, 1580, 1450, 1375, 1292, 1245, 1210, 1000, 955; ^{1}H NMR ($CDCl_3$) 7.68 (m, 20 H), 5.41 (dd, 2 H, $J \approx 11$), 4.84 (s, 1 H exch), 4.51 (dd, 1 H, J = 10 and 3), 3.62 (dd, 1 H, J = 18 and 10), 3.10 (dd, 1 H, J = 18 and 3); ^{13}C NMR, see Table I; mass spectrum 270 (6), 236 (18), 208 (8), 237 (6), 236 (18), 208 (8), 165 (4), 150 (6), 133 (9), 131 (4), 105 (100), 77 (62); CI mass spectrum (NH_3) 507 (<1), 489 (<1), 271 (20), 254 (68, $(M + 2H)^{2+}$), 239 (100), 237 (47), 105 (21).

Reaction of Benzylideneacetone (1c) with $Na_2S·9H_2O$. The literature procedure was followed and gave 3-acetyl-2,6-diphenyl-4-methylthiopyran-4-ol (**3c**): 42% yield; mp 184.5–186 °C (lit.[3] mp 185–186 °C); ^{1}H NMR ($CDCl_3$) 7.32 (m, 10 H), 4.62 (dd) superimposed on 4.56 (d, J = 12) for a total of 2 H, 4.02 (d, 1 H exch), 3.20 (d, 1 H, J = 12), 2.32–1.80 (m, 2 H), 1.70 (s, 3 H), 1.25 (s, 3 H); computer spin simulation gives δ 2.01 (J = 14.5 and 10 Hz) and δ 2.21 (J = 3 Hz); ^{13}C NMR, see Table I; mass spectrum 326 (1), 308 (4), 266 (19), 265 (100), 232 (9), 186 (11), 179 (11), 147 (12), 131 (11), 121 (18), 104 (12), 103 (15), 91 (22), 77 (11).

Reaction of Benzylideneacetophenone (1d) with H_2S/Et_3N in Ether. A solution of 10 g (48 mmol) of **1d** in 60 mL of Et_2O and 1 g of Et_3N was cooled to −70 °C, and about 10 mL of H_2S was condensed in the flask. The mixture was allowed to warm to room temperature with occasional stirring to give a white paste which was filtered and washed with ether. The solid (5 g) was treated with 8.8 mL of $CHCl_3$ and the mixture rapidly filtered to leave about 200 mg of a crystalline material, which after crystallization from EtOH had a melting point of 95–100 °C. It was identified as one diastereomer of bis(1,3-diphenyl-3-oxo-1-propyl) sulfide (**2d**; lit.[17] mp 109 °C): IR 3060, 3040, 1685, 1600, 1590, 1500, 1450, 1420, 1360, 1340, 1305, 1225, 975, 740, 675; ^{1}H NMR ($CHCl_3$) 7.80 (dd, 4 H), 7.36 (m, 16 H), 4.22 (t, 2 H), 3.38 (d, 4 H). The chloroform solution was evaporated to about one-third the original volume, EtOH was added, and the mixture was heated briefly to reflux. Cooling separated 3.5 g of white needles (mp 102–104 °C), identified as the second diastereomer of the sulfide **2d** (lit.[17] mp 109 °C): IR 3060, 3040, 1680, 1600, 1585, 1500, 1455, 1420, 1370, 1340, 1260, 1225, 1205, 1180, 970, 740, 675; ^{1}H NMR ($CDCl_3$) 7.83 (dd, 1 H), 7.40 (m, 16 H), 4.50 (t, 2 H), 3.53 (d, 4 H). The chloroform mother liquids were evaporated to dryness, and the residue was found by ^{1}H NMR to be a mixture of the two diasteromers. The original reaction mother liquors separated white needles after 1 day. After crystallization from $CHCl_3$, this solid melted at 155–157.5 °C and was identified as bis(1,3-diphenyl-3-oxo-1-propyl) disulfide (**11**; lit.[18] mp 156.5 °C); ^{1}H NMR ($CDCl_3$) 7.93 (dd, 4 H), 7.49 (apparent t, 6 H), 7.28 (s, 10 H), 4.38 (dd, 2 H), 3.65 (m, 4 H).

Reaction of 1,3-Diphenyl-1-mercaptopropan-3-one (10) with NH_3. The mercapto ketone **10**[18] (1.0 g, 4.1 mmol) was dissolved in 5 mL of $CHCl_3$, and 15 mL of EtOH was added. A vigorous stream of anhydrous NH_3 was passed through the suspension for 3 min to give a clear yellowish solution, which after 24 h separated solid 3-benzoyl-2,4,6-triphenyltetrahydrothiopyran-4-ol (**3d**). Filtration, washing with EtOH, and recrystallization from 50 mL of EtOH and just enought $CHCl_3$ to dissolve the solid at reflux gave 0.25 g (27%) of **3d**: mp 178–179 °C (lit.[17] mp 186 °C); IR 3450 (br), 3060, 3030, 2920, 1645, 1600, 1580, 1500, 1450, 1330, 1300, 1260, 1225, 1200, 1060, 1025, 990, 740, 725, 680; ^{1}H NMR ($CDCl_3$) 7.05 (m, 20 H), 5.13 (d, 1 H, exch), ~4.80 (dd, J = 10 and 4) superimposed on 4.86 (d, J = 11) for a total of 2 H, 4.48 (d, 1 H, J = 11), 2.38 (m, 2 H); computer spin simulation gives δ 2.46 (J = 14 and 11 Hz) and δ 2.28 (J = 3 Hz). ^{13}C NMR, see Table I; mass spectrum 450 (<1), 432 (<1), 327 (43), 310 (16), 242 (18), 241 (58), 209 (37), 208 (50), 207 (65), 179 (11), 149 (12), 131 (27), 105 (100), 103 (21), 77 (48).

The reaction mother liquors were added to the EtOH washings, and on being allowed to stand, the mixture separated 84 mg (9%) of a white material identified as the disulfide **11** by melting point and ^{1}H NMR analysis.

Reaction of Bis(1,3-diphenyl-3-oxo-1-propyl) Sulfide (2d) with $Na_2S·9H_2O$. A small amount of Na_2S was added to the colorless solution of 100 mg (0.22 mmol) of the diastereomer of **2d** having a melting point of 102–104 °C in 5 mL of anhydrous hot EtOH. A pale yellow coloration developed immediately, and after 5 h at room temperature filtration yielded 65 mg (65%) of the tetrahydrothiopyran-4-ol **3d**, mp 177–178 °C (after crystallization from EtOH–CH_3CN).

Similarly, 83 mg (0.18 mmol) of the diastereomer of **2d** having a melting point of 95–100 °C gave 32 mg (32%) of the tetrahydrothiopyran-4-ol **3d** as identified by ^{1}H NMR.

Reaction of Benzylideneacetophenone (1d) and Sodium Polysulfide. To 40 mL of EtOH were added alternate portions of Na_2S and S with stirring and protection from water until the total volume of the dark red solution was about 75 mL. Upon addition of 3 g (14.4 mmol) of the ketone **1d** a solution was obtained which after a few hours turned into a solid paste. After a total of 24 h the solid was filtered, stirred for 2 h with a 20% solution of $(NH_4)_2S$, and filtered again. The cake was washed with $(NH_4)_2S$ solution and then with water until the washings were colorless. Crystallization from 100 mL of AcOH with Norite treatment gave 1.5 g (47%) of 2,4-dibenzoyl-3,5-diphenyltetrahydrothiophene (**13**) as small white needles: mp 206–208 °C (lit.[17] mp 212 °C); IR 3070, 3020, 1690, 1670, 1600, 1590, 1500, 1450, 1260, 1230, 1190, 970, 750, 720, 680; ^{1}H NMR ($CDCl_3$) 7.75 (m, 2 H), 7.12 (m, 18 H), 5.02 (m, 1 H), 5.16 (m, 1 H), 4.66 (m, 2 H); ^{13}C NMR, see Table I; mass spectrum 448 (4), 343 (2), 240 (16), 239 (29), 209 (30), 105 (100), 77 (30).

Bis(3-oxo-*n*-butyl) Sulfide (2e). A stream of H_2S was bubbled through a solution of 20 g (0.29 mmol) of methyl vinyl ketone (**1e**) in 150 mL of EtOH at room temperature for 90 min with stirring. Evaporation of the solvent left 23 g of yellowish oil, which was distilled (Kugelrohr) at 100–105 °C (2 mm) [lit.[23] bp 102–107 °C (1 mm)] to give 16 g (64%) of **3e**: ^{1}H NMR ($CDCl_3$, C_6H_6) 2.52 (m, 4 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) 206.5, 43.5, 30.0, 25.9. The disemicarbazone[25] has the following: mp 189–191

°C; ^{13}C NMR (Me_2SO-d_6) 157.4, 147.7, 38.0, 27.8, 15.7. Anal. Calcd for $C_{10}H_{20}N_6SO_2$: C, 41.67; H, 6.95; S, 11.11. Found: C, 41.79; H, 7.37; S, 10.95.

Reaction of Bis(3-oxo-1-butyl) Sulfide (2e) with Na_2S. The sulfide **3e** (1.0 g, 57 mmol) was dissolved in 7 mL of dry EtOH, and a small amount of anhydrous Na_2S was added. After 24 h at room temperature, the dark orange solution was diluted with ether, washed with H_2O three times, dried, and evaporated, to leave 0.5 g of an orange oil, which was chromatographed through 14 g of SiO_2 with $CHCl_3$ as eluant. The first fraction consisted of 0.28 g (28%) of a yellow oil, identified as the tetrahydrothiopyran-4-ol **21**: IR 3500 (br), 2960, 2920, 2830, 1695, 1460, 1430, 1370, 1350, 1310, 1210, 1150, 1110, 1090, 920, 890; ^1H NMR ($CDCl_3$) 3.67 (br, 1 H), 2.23 (s), 1.16 (s), 3.20–0.93 (m); ^{13}C NMR, see Table I; mass spectrum 174 (3), 113 (3), 104 (3), 103 (2), 71 (16), 70 (15), 55 (52), 43 (100). Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.10. Found: C, 55.15; H, 7.86.

The second fraction was a yellow oil (0.15 g, 15%) identified as the tetrahydrothiopyran-4-ol **22**: IR 3450, 2820, 1695, 1420, 1350, 1200, 1160, 1135, 1100, 1080, 925; ^1H NMR ($CDCl_3$) 2.23 (s), 1.16 (s), 3.08–1.75 (m); mass spectrum 174 (2), 113 (10), 104 (3), 103 (4), 71 (19), 70 (9), 55 (35), 43 (100); ^{13}C NMR, see Table I. Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.10. Found: C, 55.08; H, 7.74.

Acknowledgment. This research was supported by grants from The Robert A. Welch Foundation and the TCU Research Foundation.

Registry No. 1a, 4070-75-1; **1c**, 122-57-6; **1d**, 94-41-7; **1e**, 78-94-4; **2d** (isomer 1), 75731-94-1; **2d** (isomer 2), 75731-95-2; **2e**, 40790-04-3; **3a**, 75731-96-3; **3c**, 23849-67-4; **3d**, 75731-97-4; **3e**, 75731-98-5; **10**, 5076-35-7; **11**, 61138-07-6; **13**, 75731-99-6; **22**, 75732-00-2; H_2S, 7783-06-4.

Supplementary Material Available: Computer simulated and actual NMR spectra of the ABX and OH portion of **3c** and **3d** (2 pages). Ordering information is given on any current masthead page.

Synthesis of (*Z*)-4-(Acylamino)- and 4-(Alkylamino)-α-oximinophenylacetic Acids: Properties and Stereochemical Determination

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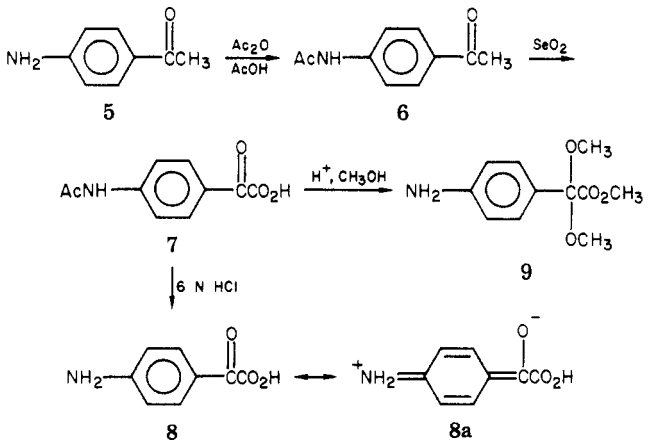
Received August 12, 1980

The preparation, properties, and stereochemical determinations of a series of 4-substituted α-oximinophenylacetic acids are described. The 4-acetamido and 4-[[(benzyloxy)carbonyl]amino]-α-oxophenylacetic acids **7** and **19** were synthesized from the corresponding acetophenones with selenium dioxide. The oximes were then prepared and their stereochemistry determined as *Z* (syn), through the chemical properties of the methoxyimino derivatives. A key intermediate was (*Z*)-methyl 4-[[(benzyloxy)carbonyl]amino]-α-[[(tetrahydro-2*H*-pyran-2-yl)oxy]imino]phenylacetate (**24**), which was synthesized from the free oxime or from the keto acid by using *O*-(tetrahydropyran-2-yl)hydroxylamine. Deprotection of this compound at nitrogen gave the 4-amino-α-oximino ester, **25**, which was acylated with a variety of acid chlorides and hydrolyzed to the 4-(acylamino)-α-oximinophenylacetic acids. By employment of methyl 4-amino-α-oxophenylacetate dimethyl ketal (**9**), a general reductive amination process was developed, leading to the 4-(alkylamino)-α-oximinophenylacetic acids.

Many novel and therapeutically significant β-lactam antibiotics have recently been developed containing the (*Z*)-α-oximino acid moiety appended to a β-lactam nucleus.[1] Most notable among these are cefuroxime[2] (**1**), cefotaxime[3] (**2**), and nocardicin A[4] (**3**) (Chart I). In all known cases, the *E* isomers were not found to be active.

Scheme I



As part of our β-lactam program, we were interested in preparing new α-oximino acids of type **4**, which bear a distinct electronic and spatial resemblance to the 4-hydroxy-α-oximinophenylacetic acid portion of **3**. The 4-amino derivative **4**, unlike its 4-hydroxy counterpart, possesses a greater potential for the elaboration of bio-

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